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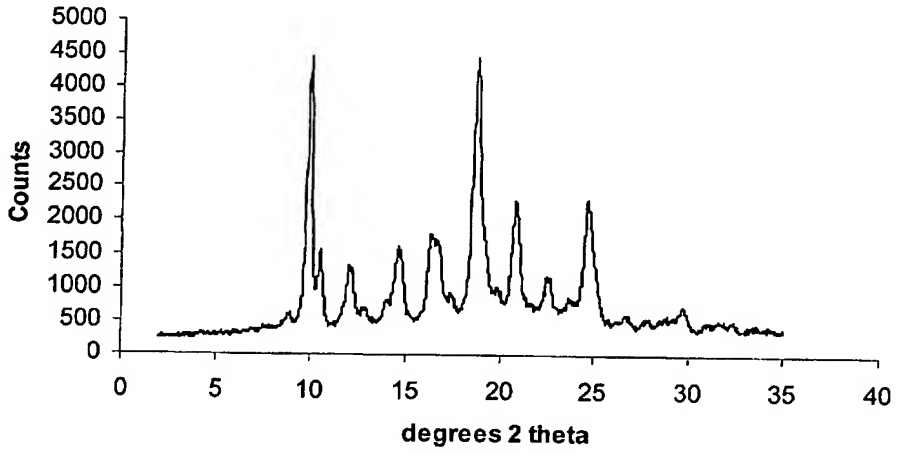
(54) Title: PROCESS FOR PREPARING CRYSTALLINE FORM I OF CABERGOLINE



(57) Abstract: A process for producing crystalline form I of cabergoline, which process comprises crystallization of the desired form from a toluene/heptane or toluene/hexane mixture starting from raw cabergoline, followed by recovery and removal of the solvent from the resulting toluene solvate Form X. The new solvate Form X of cabergoline, useful intermediate, and its preparation are also provided.

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PROCESS FOR PREPARING CRYSTALLINE FORM I OF CABERGOLINE

This application claims priority to U.S. application Serial No. 60/364,567, filed March 15, 2002, and U.S. application No. 60/410,253, filed September 12, 2002, the entirety of each of these applications are hereby incorporated by reference herein.

Cabergoline is an ergoline derivative interacting with D2 dopamine receptors and is endowed with different useful pharmaceutical activities and it is used in the treatment of hyperprolactinemia, central nervous system disorders (CNS) and other related diseases. Cabergoline is the generic name of 1((6-allylergolin-8β-yl)-carbonyl)-1-(3-dimethylaminopropyl)-3-ethylurea, described and claimed in US 4,526,892. The synthesis of cabergoline molecule is reported also in Eur. J. Med. Chem., 24,421,(1989) and in GB-2,103,603-B.

Cabergoline Form I, like cabergoline, displays a significant inhibitory effect with regard prolactine and has therapeutic properties that make it possible to treat patients who have pathological conditions associated with an abnormal prolactine level, thus is useful in human and/or veterinary medicine. Cabergoline is also active, alone or in combination, in the treatment of reversible obstructive airways diseases, for controlling intra-ocular pressure and for the treatment of glaucoma. It is also employed in the veterinary field, as antiprolactin agent and in cutting down drastically the proliferation of vertebrate animals. The several uses of cabergoline are for example described in WO99/48484, WO99/36095, US5705510, WO95/05176, EP040,325.

Cabergoline Form I is particularly useful in the treatment of Parkinson's disease (PD), Restless Legs Syndrome (RLS), treatment of diseases like Progressive Supranuclear Palsy (PSP) and Multysystemic atrophy (MSA).

Crystalline cabergoline Form I, an anhydrous not solvated form of cabergoline, was firstly prepared by crystallization from diethyl ether, as described in Il Farmaco, 50 (3), 175-178 (1995).

Another process for preparing crystalline Form I of cabergoline through a toluene solvate Form V was described in WO01/70740.

For purposes of lowering the cost of the bulk, it is highly desirable to improve the yield of the industrial production of crystalline Form I of cabergoline and to avoid lengthy process. Therefore, it is an objective of the present invention to obtain a highly pure Form I of

cabergoline using an organic solvent system that has never been heretofore used. Efficiently preparing highly pure cabergoline in crystalline Form I provides benefits with respect to industrial costs and environmental considerations.

The present invention concerns a new process for preparing crystalline Form I of cabergoline.

The method of the present invention comprises the preparation of a new toluene solvate of cabergoline and its exclusive conversion into crystalline Form I of cabergoline. The new toluene solvate of cabergoline is a crystalline form fully characterized herein below, but it is referred to for convenience as "Form X".

In another aspect, the invention provides solvated crystalline Form X of cabergoline that, when de-solvated, can quickly and exclusively yield crystalline Form I of cabergoline.

In a fourth aspect, the invention provides processes for preparing solvated crystalline Form X of cabergoline and a process for preparing crystalline Form I of cabergoline from solvated crystalline Form X of cabergoline.

FIG. 1 is an x-ray powder diffraction (XRD) pattern showing peaks characteristic of crystalline cabergoline solvate Form X, made in accordance with Example 1.

FIG. 2 is an x-ray powder diffraction (XRD) pattern showing peaks characteristic of crystalline cabergoline Form I, according to Example 2.

FIG. 3 is an x-ray powder diffraction (XRD) pattern showing peak characteristic of the original toluene solvate, referred to as Form V made in accordance with procedure outlined in WO01/70740.

FIG. 4 is a differential scanning calorimeter (DSC) profile of Form X, showing thermal event associated with eutectic melting of cabergoline with toluene.

FIG. 5 is a differential scanning calorimeter (DSC) profile of Form V, showing thermal event associated with eutectic melting of cabergoline with toluene

FIG. 6 is the time resolved powder x-ray data of the de-solvation phase transformation of Form X at 43^{o} C under high vacuum (94.8 kPa).

According to the present invention, Form I can be readily prepared starting from crude material by crystallization from a toluene/heptane or toluene/hexane mixture, through a new solvate Form X of cabergoline. The present process for preparing Form I shows advantages with respect to the old ones because of the rapid and exclusive conversion of solvate Form X of cabergoline into Form I. The new solvate Form X of cabergoline, a

novel gel-mediated process for its preparation and a process for its conversion into crystalline cabergoline Form I are also provided.

Characterisation

X-ray powder diffraction (XRD) was used to characterise the new solvate Form X of cabergoline and compare it to Forms I and V. The de-solvation and phase conversion of form X to form I was studied by studying the solvate in a special cell on the X-ray diffractometer at elevated temperatures under high vacuum over a period of time. Differential scanning calorimeter (DSC) profiles were also obtained for Forms V and X to show the distinct nature of these solvates.

X-ray diffraction analysis

Powder X-ray diffraction was performed using either a Siemens D5000 powder diffractometer or an Inel multipurpose diffractometer. For the Siemens D5000 powder diffractometer, the raw data were measured for 2θ (two theta) values from 2 to 50, with steps of 0.020 and step periods of two seconds. For the Inel multi-purpose diffractometer, samples were placed in an aluminium sample holder and raw data were collected for one thousand seconds at all 2θvalues simultaneously. The data so obtained are shown in the tables I to III herein below.

A special cell that could be heated and evacuated through a vacuum pump was used to study the de-solvation and phase conversion behaviour of Form X to Form I on the Inel multi-purpose diffractometer. The de-solvation and phase conversion behaviour of Form X to Form I was studied at

43° C and 94.8 kPa vacuum. The very high vapour pressure of toluene necessitated high vacuum for efficient solvent removal. For the de-solvation and phase conversion of Form X to Form I, the Inel multi-purpose diffractometer was programmed to collect X-ray diffraction data for ten minutes every half an hour for a total experimentation time of two hours and forty minutes (including data collection).

The x-ray powder diffraction pattern for solvate Form X (Figure 1) shows a crystalline structure with useful distinctive peaks as depicted in the following table I.

Table I X-Ray diffraction data, Form X

Angle 2θ	Intensity Cps X 1000	Intensity %
7.988	6899	100.00
10.937	837	11.97
12.067	477	6.82
14.927	2213	31.66
17.162	2603	37.25
17.320	3163	45.26
19.938	855	12.22
21.075	2720	38.92
23.892	1371	19.61
26.779	1086	15.54

The x-ray powder diffraction pattern for cabergoline Form I (Figure 2) shows a crystalline structure with distinctive peaks depicted in the following table II.

Table II X-Ray diffraction data, Form I

Angle 2θ	Intensity Cps X 1000	Intensity %
9.870	4458	99.86
10.497	1498	33.55
12.193	1244	27.86
14.707	1556	34.86
16.658	1743	39.94
16.721	1644	36.83
18.707	4464	100.00
20.822	2330	52.19
22.688	1172	26.25
24.652	2341	52.44

The x-ray powder diffraction pattern for the known toluene solvate Form V of cabergoline (Figure 3) described in WO01/70740 has a crystalline structure with distinctive peaks depicted in the following table III

Table III X-Ray diffraction data, Form V

Angle 2θ	Intensity Cps X 1000	Intensity %
8.866	5930	100.00
12.287	705	11.88
16.375	1440	24.28
18.171	1169	19.71
18.991	1167	19.67
21.043	1214	20.47
24.938	751	12.66

These data clearly indicate that cabergoline Form X is a new crystalline polymorph solvate easily distinguishable by XRD from the known solvate V described in the prior art.

The de-solvation and phase transformation behaviour of Form X to Form I under the aforementioned conditions (Figure 6), shows that most of Form X, which is characterised by its main peak at 7.988 degrees 2 θ had transformed to Form I (characterised by 9.870 and 18.707 degrees 2 θ peaks) within thirty minutes. The transform was complete within one hour as indicated by the complete disappearance of 7.988 degrees 2 θ peak.

Figure 6 clearly shows the favourable kinetic of de-solvation and phase transformation from Form X to Form I. This data also demonstrates the very significant short time for making Form I through Form X.

Differential Scanning Calorimeter analysis (DSC).

Differential scanning calorimeter profiles were obtained from a Mettler-Toledo 822^e differential scanning calorimeter. The data was collected between 25 and 150^O C at a heating ramp of 10^O C/min. Forty micro-liter hermetically sealed aluminium pans with a pinpricked hole in the lid were used.

Differential scanning calorimeter profile for Form X (Figure 4, shows a major endothermic thermal event centred around 53^O C, followed by a minor and broad endothermic thermal event centred around 74^O C. The former corresponds to eutectic melting of Form X with toluene, while the latter could be associated with the gradual loss of toluene through vaporization. For the purposes of this invention eutectic melting is defined as the transformation of solvent containing solids into a homogeneous liquid solution without any significant loss of solvent associated with the solids.

Differential scanning calorimeter profile for Form V (Figure 5) shows a single endothermic thermal event centred around 66^O C. This thermal event corresponds to the eutectic melting of Form V in toluene.

Comparison of Figures 4 and 5 also shows the distinct nature of Forms X and V.

The process of the present invention for producing crystalline cabergoline Form I is characterized by crystallization from toluene/heptane. Hexane can also be used instead of heptane. Heptane is however, preferred for its toxicological properties, which are better suited for pharmaceutical application.

The process comprises dissolving cabergoline in a suitable amount of toluene, preferably in an amount of from 2.5 to 4.0 g of toluene per gram of cabergoline, more preferably about 3.5 g of toluene per gram of cabergoline, at room temperature.

The cabergoline used as starting material can an oil obtained through the synthesis described in Eur. J. Med. Chem.,24, 421,(1989), or can be any crystalline form of cabergoline or mixture thereof, including Form I crystals, obtained from the procedures described in the aforementioned references.

The resulting solution is cooled to temperatures below –10 °C and stirred overnight, preferably for a minimum of 18 hours.

During the overnight hold period the solution of cabergoline in toluene turns into a gel, which for the purposes of this invention is defined as a thick non-Newtonian suspension of bi-refringent solids in equilibrium with a saturated solution within the suspension.

Cold heptane or hexane, preferably around 10 to 20 g per gram of cabergoline in the gel phase, is then added to the gel. This addition of cold heptane or hexane is termed as the "quenching" of the gel phase. It refers to very strong anti-solvent properties of heptane or hexane for cabergoline toluene solutions. These properties essentially help freeze a solid suspension like the aforementioned gel, in a given solid state by eliminating the driving force for subsequent solid phase conversions to crystalline forms that may be more stable than Form X.

Upon the addition of heptane or hexane the gel turns into easily suspendable slurry, which is stirred at sub-ambient temperatures. Under these conditions, the toluene solvate Form X is obtained, that may be recovered by common procedures, for example by filtration under reduced pressure or by centrifugal filtration, followed by washing of the solids with pure heptane or hexane to remove residual mother liquor and free toluene. The resulting crystals of Form X are very unstable when removed from their mother liquor and essentially convert to Form I without applying any heat under ambient storage within twenty four hours.

Form I crystals obtained in this particular manner, however, may contain residual toluene at levels unacceptable for pharmaceutical use and therefore preferably the solids are heated in a vacuum oven for lowering toluene content to within the acceptable range. This drying process can be accomplished by any suitable means such as, but not limited to, heating the solids, reducing the ambient pressure surrounding the solids, or combinations thereof. The drying pressure and time of drying are not narrowly critical. The drying pressure preferably is about 101 kPa or less. As the drying pressure is reduced, however, the temperature at which the drying can be carried out and/or the time of drying likewise is reduced. Particularly for solids wet with high boiling solvents like toluene, drying under vacuum will permit the use of lower drying temperatures. The optimum combination of pressure and

temperature is usually determined from the vapour pressure versus temperature diagram for toluene and operational factors related to the design of the dryer. The time of drying need only be sufficient to allow for the reduction in the level of toluene to a pharmaceutically acceptable level. When the solids are heated to remove the solvent, such as in an oven, a temperature that preferably does not exceed about 150°C is selected.

Alternatively, Form I cabergoline can be prepared directly from the solvated crystalline Form X obtained immediately after filtration through a combined de-solvation and drying step. Given the exceedingly fast kinetics of de-solvation and phase conversion of Form X to Form I, this combined operation can be conducted without requiring any modifications to the schematics of the drying process described in the preceding paragraph.

The crystals of Form I of cabergoline prepared according to the process of the present invention have preferably a polymorph purity > 95%, more preferably >98% at yields in excess of 90% w/w, compared to about 60% for the route described in WO01/70740.

Toluene solvate Form X is also object of the present invention. The x-ray powder diffraction pattern for Form X (Figure 1) shows a crystalline structure. These data indicate that cabergoline solvate Form X is easily distinguishable by XRD and DSC. The solvate X of this invention is a true solvate having a fixed composition of about 0.5 toluene moles per mole of cabergoline. The significant differences with the known hemi solvate form described in WO01/70740 can be readily appreciated looking at the respective XRD and DSC spectra.

The following Examples contain detailed descriptions of methods of preparation of solid state forms of cabergoline described herein. These detailed descriptions fall within the scope of the invention and illustrate the invention without in any way restricting that scope. All percentages are by weight unless otherwise indicated.

Example 1. Preparation of solvated crystalline Form X of cabergoline.

3 g of cabergoline were dissolved in 10.5 g of toluene in a 125 mL jacketed reactor equipped with an overhead agitation system. Once a clear solution had formed under agitation at 142 revolutions per minute, the reactor was cooled to a set point of –18 °C in order to achieve a temperature of –15 °C in the reactor. The solution was stirred overnight (a minimum of 18 hours). During this period it turned into a thick gel. In a separate reactor 45 g of heptane were cooled to –15 °C and then transferred to the reactor containing the gel over a period of fifteen minutes. The resulting slurry was stirred at –15 °C for three and a half hours before being discharged onto a filtration flask operating under reduced pressure.

The cake was washed with 6 mL of heptane to remove mother liquor and wash away excess toluene from the solids. These solids were left of the filter for thirty minutes.
They were identified as Form X by XRD, data shown in figure 1 and in table 1. Yield was about 102%(w/w) on the basis of initial content of pure "toluene free" cabergoline.

Example 2. Preparation of crystalline Form I of cabergoline.

The crystal solvate Form X obtained in example 1 was placed in vacuum oven under 94.8 kPa of vacuum at ambient temperature for two hours. The temperature was then increased to 43 ^{O}C and the solids were further dried for 24 hours. Another 24 hours of drying was afforded at
60 ^{O}C. XRD and solvent content analysis on the solid samples pulled after each phase of the drying indicated that solids had converted to Form I after first phase of drying (at ambient temperature and high vacuum), however the toluene content was not within the specifications on the product. The solids met all the product specifications after the second phase of drying (24 hours at 43 ^{O}C under high vacuum). After drying, the resultant crystal Form I was identified by XRD data shown in Figure 2. The overall yield was about 93% on the basis of pure cabergoline initial content. The assayed polymorph purity was >98%.

We claim:

1. A process for producing crystalline Form I of cabergoline, which process comprises the preparation of toluene solvate Form X of cabergoline and its conversion into crystalline Form I of cabergoline.

2. A process according to claim 1 in which the the preparation of toluene solvate form X comprises dissolving cabergoline in a suitable amount of toluene, cooling and stirring the resulting solution, quenching the resultant gel with cold heptane or hexane, collecting the resulting solvate form X of cabergoline having the XRD powder pattern of Figure 1 and converting the solvate form X into cabergoline Form I by storage at room temperature and/or by drying.

3. A process according to claim 2 in which the suitable amount of toluene is from 2.5 to 4.0 g of toluene per gram of cabergoline.

4. A process according to claim 2 in which the suitable amount of toluene is about 3.5 g of toluene per gram of cabergoline.

5. A process according to claim 2 in which cabergoline used as starting material is an oil, a crystalline form or mixture thereof.

6. A process according to claim 2 in which the solution of cabergoline in toluene is cooled to a temperature below $-10\ ^{o}C$ and stirred overnight.

7. A process according to claims 2 to 6 in which the resultant gel is quenched with cold heptane.

8. A process according to claim 7, in which the cold heptane is added to the gel in an amount of from 10 to 20 g of heptane for each gram of cabergoline.

9. A process according to claim 2 in which the final drying is carried out by heating the solids of the solvate form X, reducing the ambient pressure surrounding the solids, or combinations thereof.

10. A process according to claim 2 characterized in that the de-solvation and the drying steps are combined.

11. Solvate form X of cabergoline having the XRD powder pattern of Figure 1.

12. Solvate form X of cabergoline having the distinctive peaks in the powder X-ray diffraction shown in the following table I:

Angle 2θ	Intensity Cps X 1000	Intensity %
7.988	6899	100.00
10.937	837	11.97
12.067	477	6.82
14.927	2213	31.66
17.162	2603	37.25
17.320	3163	45.26
19.938	855	12.22
21.075	2720	38.92
23.892	1371	19.61
26.779	1086	15.54

13. A process for producing solvate form X of cabergoline as defined in claim 11 or 12, which process comprises dissolving cabergoline in a suitable amount of toluene, cooling the resulting solution and stirring it under agitation, quenching the resultant gel with cold heptane or hexane, and collecting the resulting solvate form X of cabergoline.

14. A process according to claim 13 in which the in which the resultant gel is quenched with cold heptane.

15. A process according to claim 14 in which the in which the amount cold heptane added for quenching the gel is from 10 to 20 g for each gram of cabergoline.

Figure 1

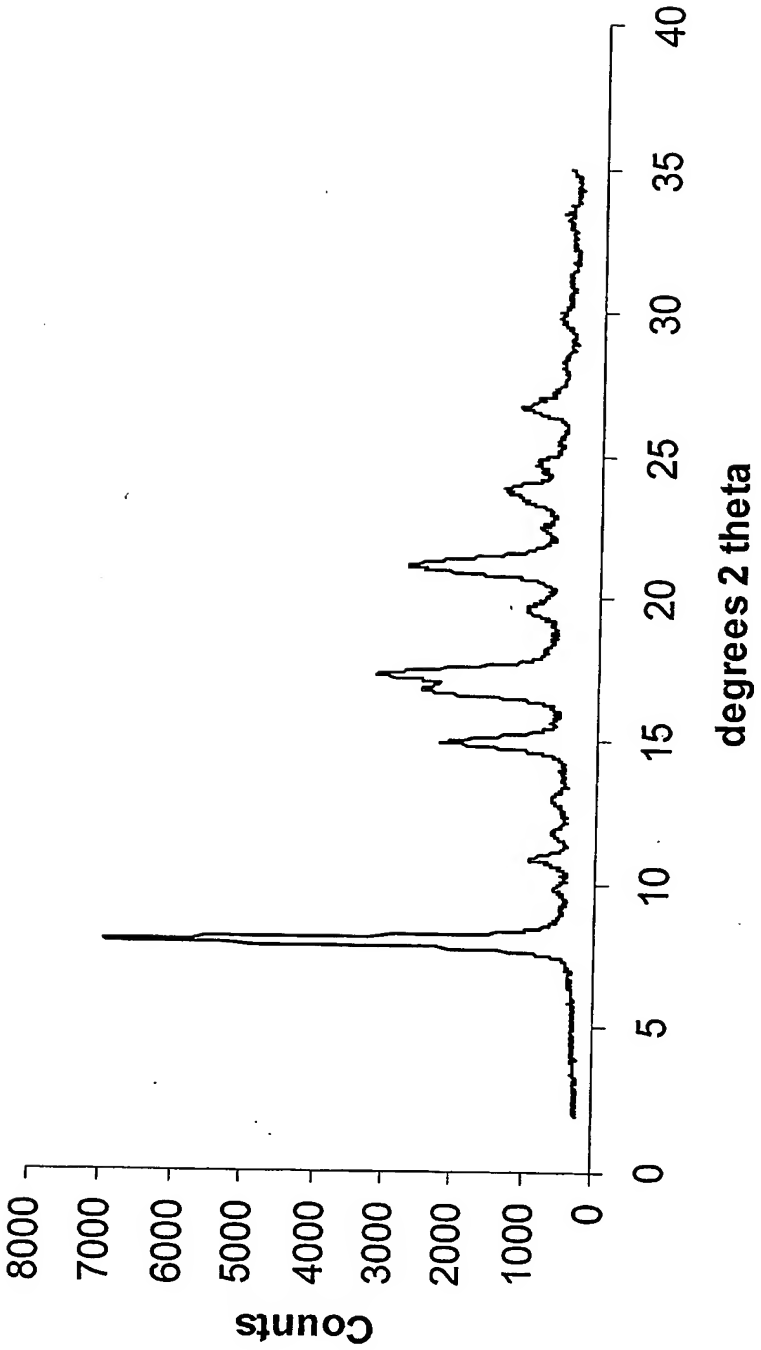
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Figure 2

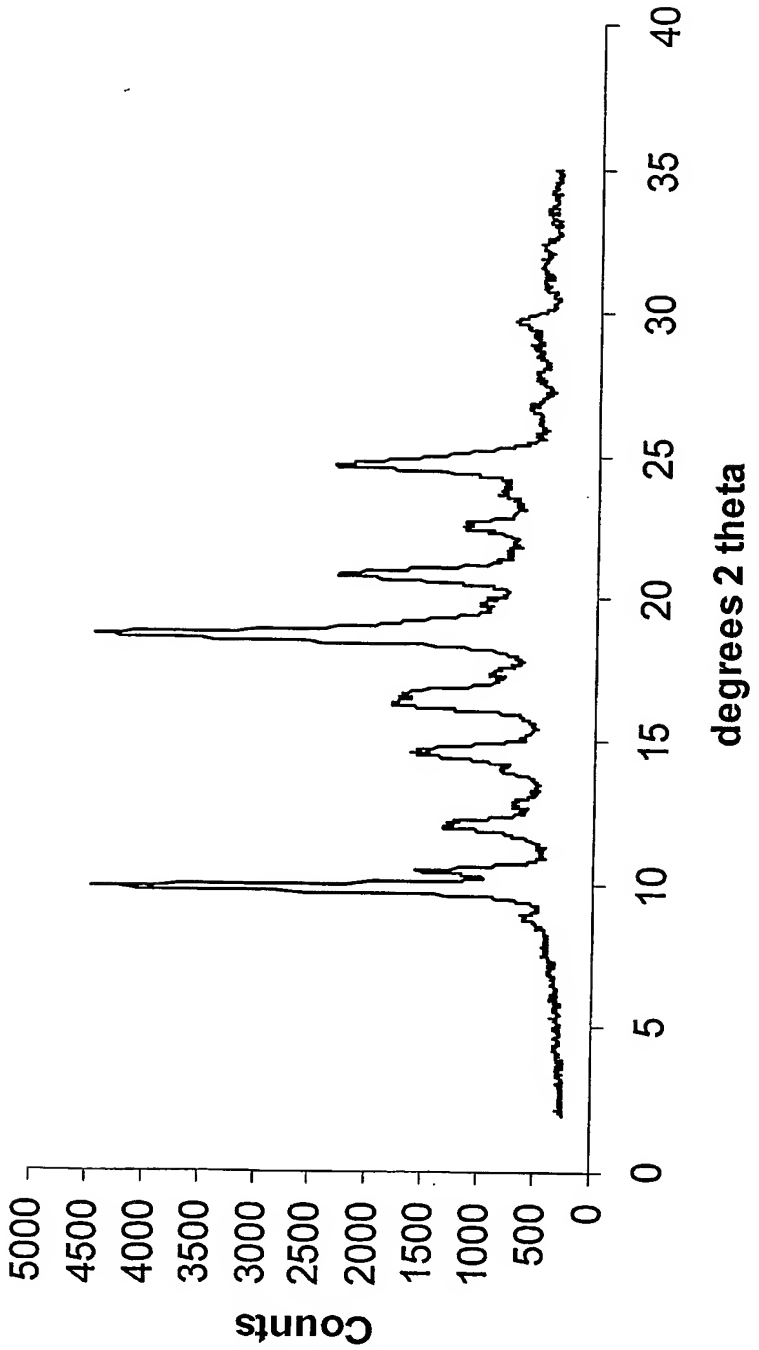
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Figure 3

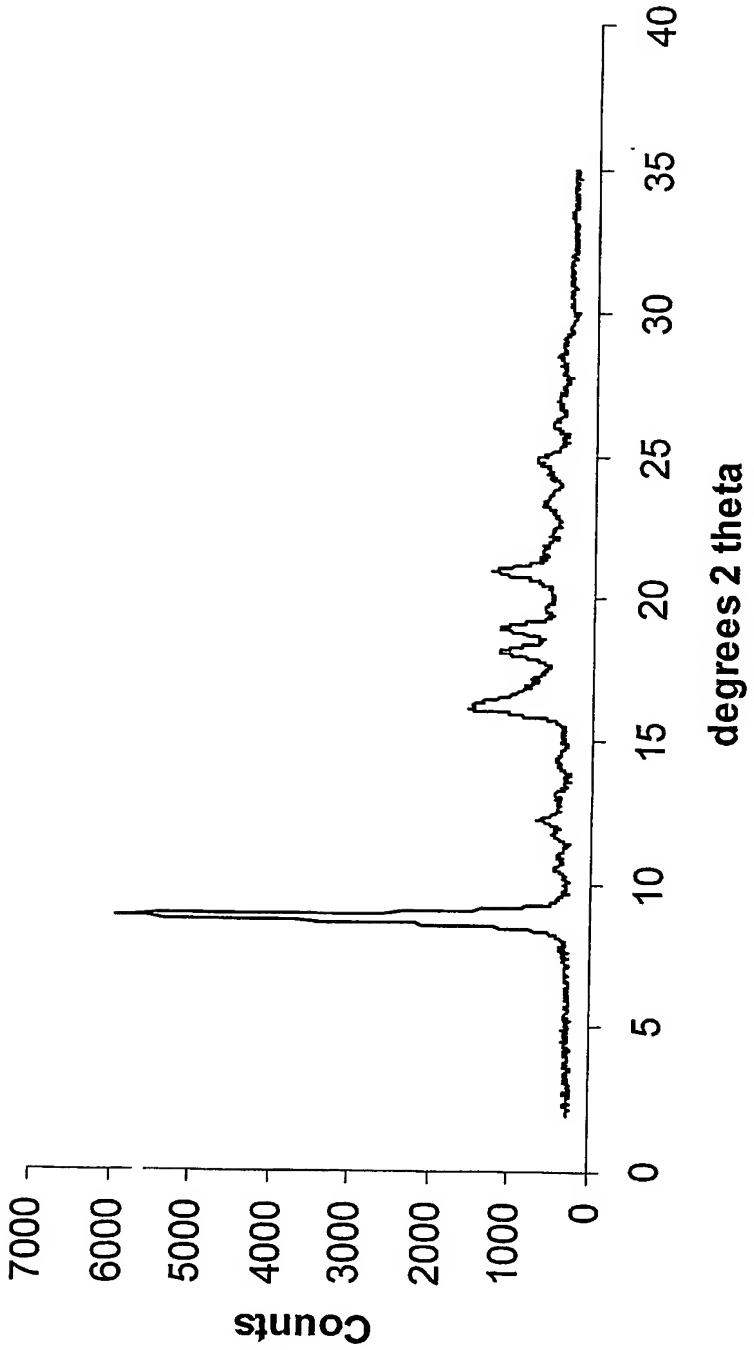
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Figure 4

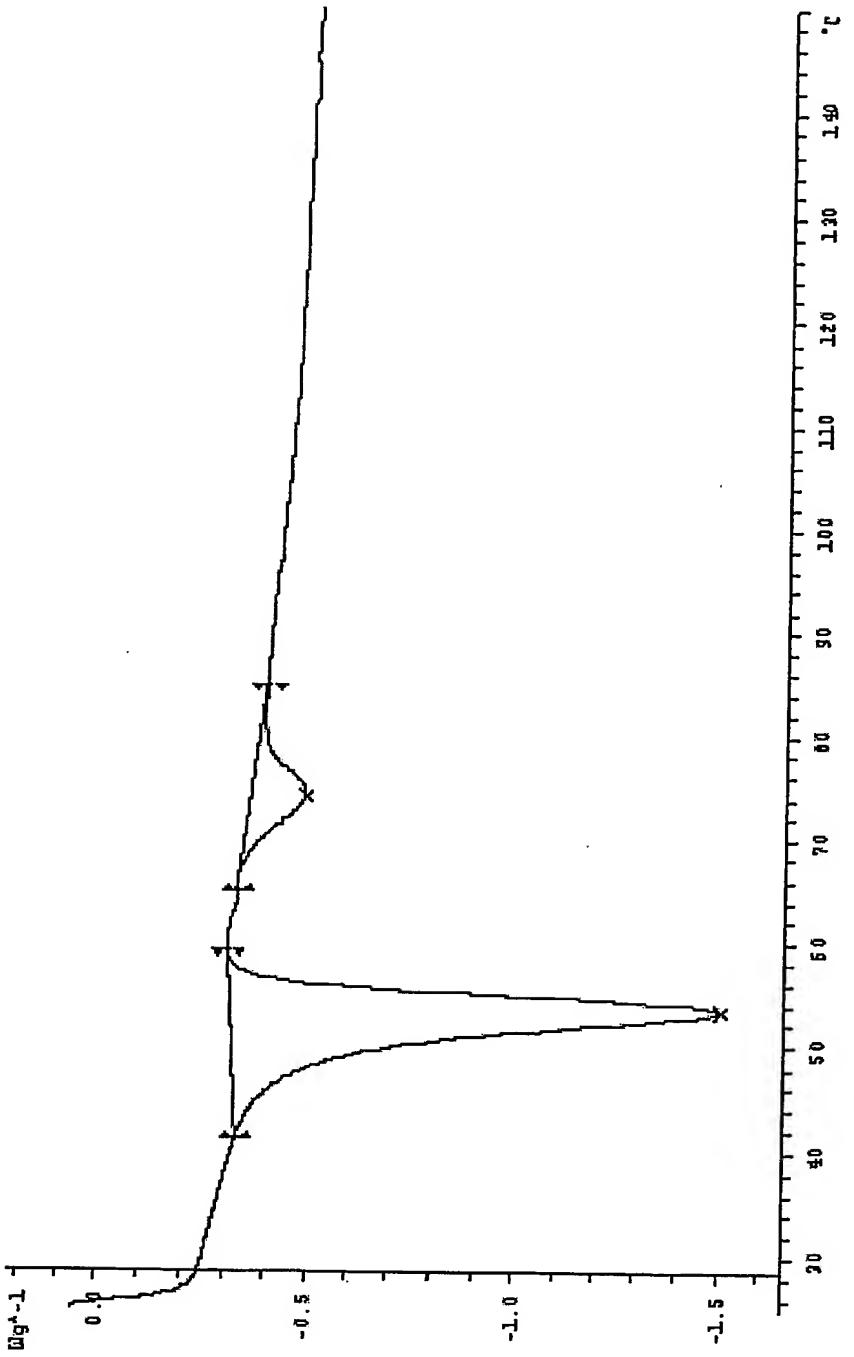


Figure 5

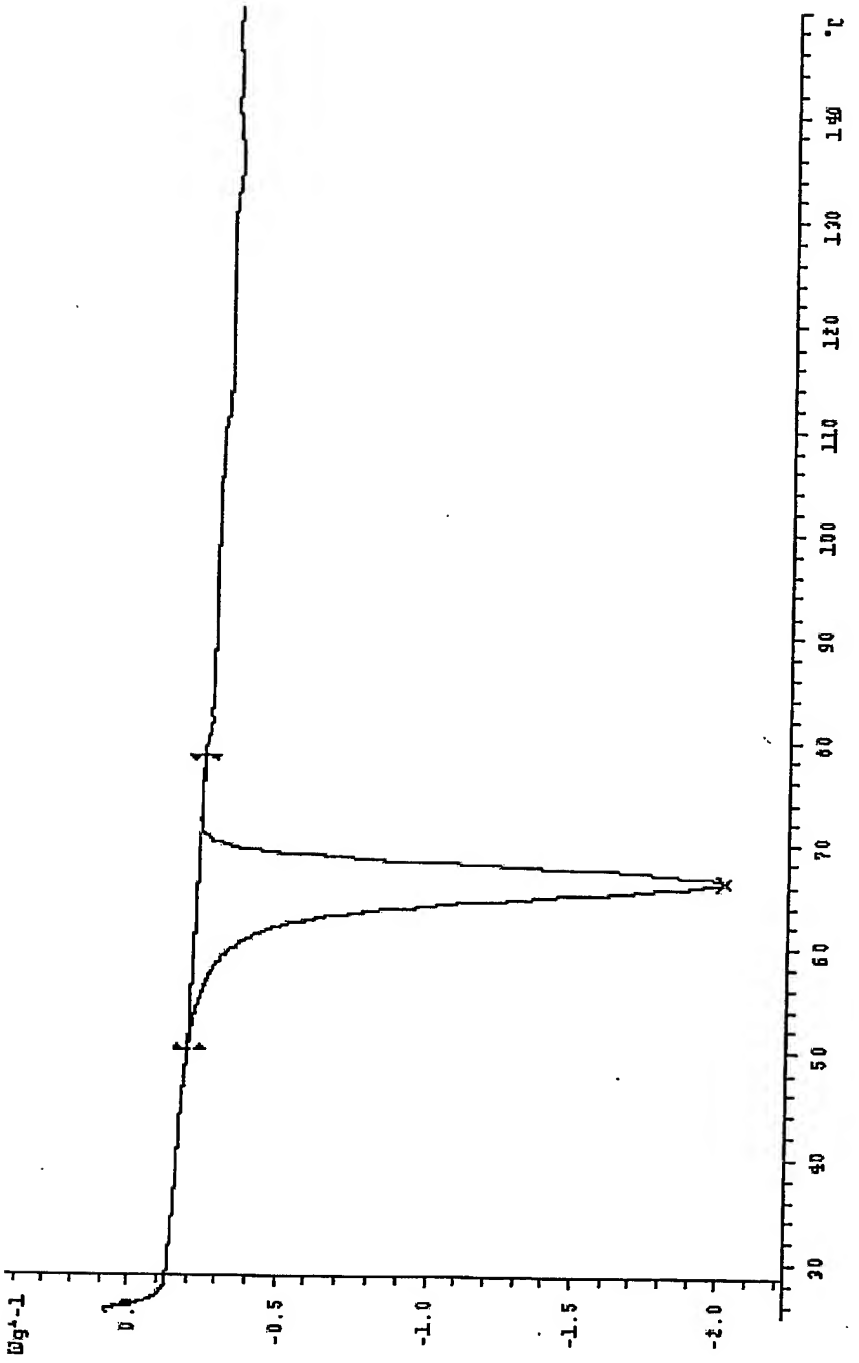
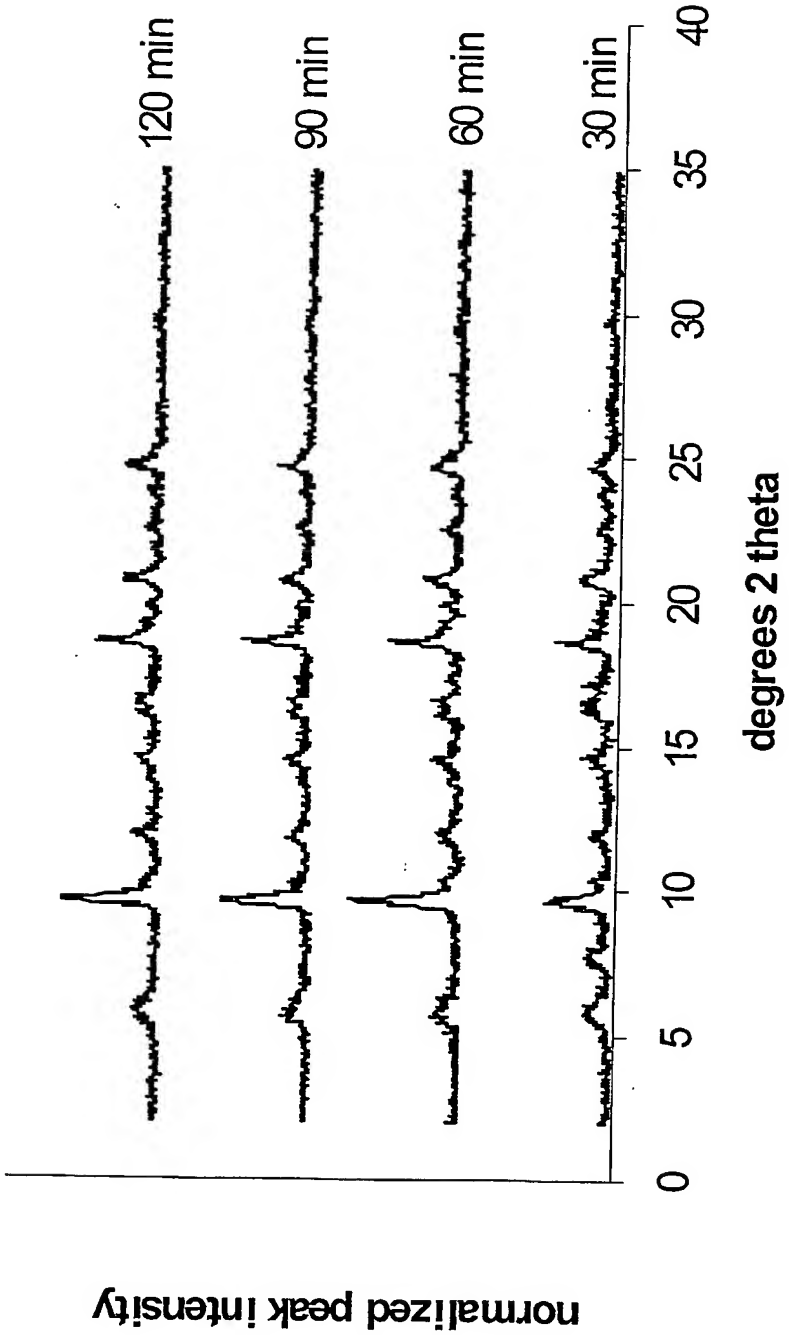


Figure 6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